Non-technical Abstract

Lung inflammation is important in the development of lung disease in CF and the dominant inflammatory cell found in the lungs of patients with CF is a white blood cell called a neutrophil. The neutrophil produces a protein, called elastase, which is capable of digesting the lung as well as enhancing the function of other mediators of inflammation. Normally, the body produces proteins, called antiproteases, which neutralizes the elastase. However, in CF, these normal host defenses, particularly the antiprotease α-1 antitrypsin (AAT), are overwhelmed by the inflammatory burden and cannot protect the lung from the injurious effects caused by the neutrophils. Augmentation therapy with AAT has been proposed to restore the normal protease/antiprotease balance in CF. However, it has been difficult to prove clinical efficacy of antiprotease therapy in CF patients, mainly because of a limited supply of purified antiprotease protein.

Normally, the AAT protein is made in the liver and reaches the lungs through the circulation. Lung cells themselves do not make the AAT protein and therefore its site of action is outside the lung cells. We believe that AAT gene therapy (as opposed to AAT protein therapy) is a better strategy for restoring antiprotease defense mechanisms because expression of the AAT gene inside lung cells may, in addition to neutralizing neutrophil elastase, provide additional antiinflammatory effects. This antiinflammatory effect is due to the intracellular location of AAT within the lung cells where it can prevent important reactions in the inflammatory cascade. Therefore, placing the gene inside the lung cells potentially would inhibit these inflammatory reactions, providing significant antiinflammatory activity, whereas administration of the antiprotease protein would not produce this effect because it is too big to enter the lung cells.

We are developing the nasal lavage model as a means of studying the inflammatory response of the respiratory tract in humans. In this proposal, we plan to define the inflammatory state of the nasal cavity more thoroughly in CF patients by comparing the amount of inflammation found in CF subjects noses compared to healthy volunteers. Once the inflammatory state of the CF nasal cavity is characterized, two hypotheses will be tested. The first hypothesis is that the AAT gene can be effectively delivered to the nasal cavity in CF subjects using liposomes and the second is that expression of the AAT gene locally in the respiratory tract will suppress the inflammatory response. Specifically we propose: 1. To characterize the inflammatory state of the nasal mucosa in patients with CF compared to healthy volunteers by: a) measuring in nasal lavage fluid the concentrations of inflammation-related cytokines, AAT protein, free elastase, and collagen degradation products; and b) determining in nasal mucosal scrapings the numbers of inflammatory cells present and which inflammation-related genes are expressed. 2. To determine whether the AAT gene can be delivered to the nasal mucosa of patients with CF using liposomes and to define the magnitude and time course of gene expression. 3. To determine whether transfer of the AAT gene to the nasal mucosa of patients with CF decreases inflammation and production of proinflammatory molecules.